REMARKS

Claims 1-14 are pending. Applicants have amended claim 1. Support for the amendments can be found throughout the specification and in the claims as originally filed. Applicants make these amendments without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter. No new matter is introduced by these amendments.

Claims Rejections – 35 U.S.C. §112, second paragraph

Claims 1-5 and 9-14 are rejected, allegedly due to indefiniteness. Applicants traverse, but have amended claim 1 as follows. As an initial matter, the structures of Formulae (I) and (II) are replaced to comport with those delineated at page 4 of the specification as filed. Thus, what previously appeared as R_7, R_8 in Formula (I) and R_3 and R_4 in Formula (II), now appears as R_5 and R_6, and R_5 and R_6 in Formula (I) and (II), respectively. This is supported throughout the specification as filed including at page 4 and the examples.

Variable R_3 is removed in Formula (II) and replaced with R_5. Support for this amendment appears throughout the specification as filed including at page 4.

The term "Each" which was previously capitalized in claim 1 is now amended to read "each".

Variables R_7 and R_8 are now delineated in claim 1. Support for this amendment appears throughout the specification as filed including at pages 3-6, and claims 1-3 as filed. As such, claims 2 and 3 no longer lack antecedent basis in claim 1, from which they both depend.

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In regard to the rejection of claims 12-14 on the alleged basis that the nature of the recited agents are not known, Applicants traverse. Claims 12-14 recite anti-HCV agents. Applicants submit that one of ordinary skill would understand and appreciate the metes and bounds of an anti-HCV agent according to any of claims 12-14. For example, an anti-HCV agent is any agent that demonstrates HCV inhibitory activity, including those with demonstrated activity in standard assays such as those delineated in Examples 80 and 81 in the specification as filed. Such compounds include α-interferon, β-interferon, ribavarin, and adamantine as delineated in the specification as filed, and also include agents known in the art, including those delineated in "HCV Anti-viral Agents", Griffith et al., *Annual Reports in Medicinal Chemistry*, Vol. 39, pp.223-237 (2004) (copy attached) and references cited therein, which describe various types of inhibitors, including those delineated in instant claims 12-14. As such, Applicants submit that claims 12 –14 are not indefinite to one of ordinary skill in the relevant art and respectfully request withdrawal of the rejection.

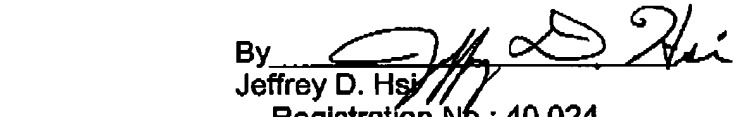
Based on the foregoing amendments and reasoning, Applicants submit that the rejections should be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be in condition for allowance, the Examiner is requested to call Applicants' undersigned representative to discuss the application. Applicants thank the Examiner in advance for this courtesy.

The Director is hereby authorized to charge any credits or deficiency in the fees filed (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. (50530) 60583.

Dated: May 1, 2006

Respectfully submitted,

By 

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HCV Anti-viral Agents

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Contents

1. INTRODUCTION

Chronic infection with HCV has become a major health problem associated with liver cirrhosis, hepatocellular carcinoma and liver failure. An estimated 170 million chronic carriers worldwide are at risk of developing liver disease [1]. In the US alone 2.7 million are chronically infected with HCV and the death-toll in 2000 was estimated between 8000 and 10,000, a number that is expected to increase significantly over the next years [2]. Considering the slow course of the infection and the nature of the current, insufficient therapy, treatment of HCV-related illness is a heavy burden on any public health system. Current therapy involving pegylated interferon-α alone (Pegasys, PEG-Intron™) or in combination with ribavirin (1) (Rebetrol™, Copegus™) [3], is expensive, associated with side-effects and exhibits only modest success rates, which are strongly dependent on the particular genotype of the virus. For the most prevalent HCV subtypes in the US, 1a and 1b (72%), the above co-therapy yields response rates between 40 and 60%. Note that the above therapy is not aimed at inhibiting viral targets directly, in contrast to the successful approaches in HIV therapy. Future therapies need to include the more elusive HCV subtypes and should benefit from targeting viral replication directly. HCV is a small, enveloped virus with a single strand RNA genome coding for a 3000 a.a. polyprotein which is processed into at least 10 individual viral proteins of which the six C-terminal ones are non-structural proteins termed NS2, NS3, NS4a, NS4b, NS5a and NS5b [4]. Assembly of the final

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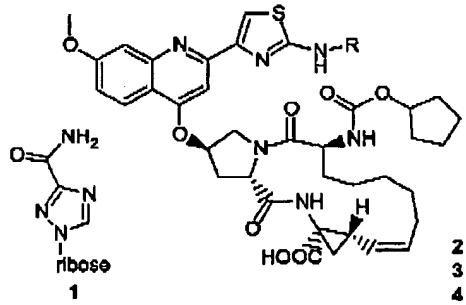
replication complex around the NS5b RNA polymerase requires five proteolytic steps of which the first is carried out by the metalloprotease NS2. Subsequently, the protease module of NS3 delivers the remaining cuts which most require NS4a as a cofactor for NS3. Fueled by the success of targeting the HIV protease and reverse transcriptase, the largest anti-HCV drug discovery efforts have been directed towards NS3 protease and NS5b RNA polymerase.

2. INHIBITORS OF VIRAL PROTEIN TARGETS

2.1. NS3 protease

NS3 is a relatively small serine protease of the chymotrypsin family and peptide sequence requirements for both efficient cleavage and competitive inhibition are well known [5]. Since low micromolar inhibition could be achieved with hexapeptides derived from N-terminal P-site cleavage products [6], the vast majority of work has not strayed from competitive peptidic inhibitors with either a covalent ('serine traps') or non-covalent mode of interaction. Most promising is the group of constrained tripeptides, **2–5**, which arose from linking the P1 and P3 a.a. side chains and optimization of the P2 proline substituents [7]. Trailblazer BILN-2061, **2**, yielded clinical proof-of-concept data as its outstanding *in vitro* activity in enzyme inhibition assays (K_i = 0.3 and 0.7 nM for subtype **1a** and **1b**, respectively) and the surrogate cell-based replicon assay (EC_{50} = 3 and 4 nM for subtype **1a** and **1b**, respectively) was mirrored by a dramatic 2–3 $\log_{10}$ reduction of viral loads within 24 h in the majority of patients that had received **2** (200 mg in an oral solution of a PEG 400/ethanol 80:20 mixture, twice-daily for 2 days) [8]. While **2** was well tolerated up to 2000 mg and no serious clinical or laboratory findings were obtained in a human safety study, further clinical trials are currently on hold because cardiac lesions were observed in routine chronic safety testing in monkeys at supra-therapeutic doses [9,10]. The primary interaction site of BILN 2061 with NS3, as revealed by a crystal structure, involves largely the residues conserved across HCV subtypes [7]. This explains why K_i values for subtypes **2a**, **2b** and **3a** are still below 100 nM. Oral bioavailability for **2** was below 20% in rats and rhesus monkeys; for dogs, values were as high as 38% [8]. Some of the clinical activity of **2** might in fact be the restoration of the IFN related cellular anti-viral response. NS3 has been shown to mediate



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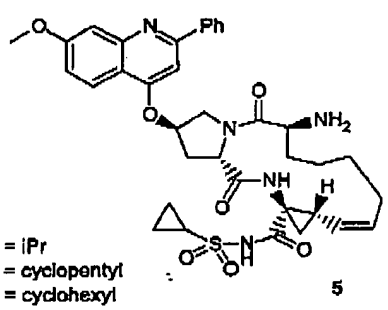
2 R = iPr
3 R = cyclopentyl
4 R = cyclohexyl



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inhibition of the phosphorylation, hence activation of IFN regulatory factor-3 (IRF-3), a key anti-viral signaling molecule [11].

The scaffold of **2** tolerates small changes in several places. IC_{50} and replicon EC_{50} values of **3** and **4** are both below 10 nM [12]. When the carboxylate group in **3** is replaced by a cyclopropyl-acylsulfonamide moiety no loss in activity is observed. This latter class of macrocycles is further exemplified by **5**, which exhibits IC_{50} and EC_{50} values of 21 nM and 124 nM, respectively [13]. Note that an unprotected amino group and a shortened aliphatic linker are compatible with good potency. Also unconstrained proline-substituted tripeptides, **6–10**, retain activity. **6** represents a group of compounds wherein various bulky aliphatic substituents (e.g., *t*-butyl, cyclobutyl, cyclopentyl, and cyclohexyl) can be interchanged [13,14]. In this scaffold, the carboxylate group can be replaced by methyl- and phenyl-acylsulfonamide moieties. A wide range of six-membered and especially five-membered heterocycles, exemplified by **7** and **8**, can be used in conjunction with the acylsulfonamide grouping [13]. **9** and **10** are examples of a large group of compounds with both IC_{50} and EC_{50} below 100 nM in which the heterocyclic proline-substituent assumes a range of substituted condensed ring systems [15]. Studies with acylsulfonamide-bearing hexapeptides demonstrated that a cluster of carboxylate groups at the N-terminus contributes greatly to inhibitory activity; **11** exhibited an IC_{50} value of 3.8 nM [16]. Among the non-covalent NS3 inhibitors, two non-peptidic natural products, **12** and **13**, showed submicromolar inhibition [17].

The class of covalent inhibitors is largely comprised of peptides bearing a reactive center at the cleavage site trapping the hydroxyl of Ser139, i.e., α-keto, aldehyde, boronic acid or lactam moieties. Most advanced is VX-950, **14**, which binds slowly and covalently ($K_i^* = 3$ nM, $T_{1/2} = 58$ min), yet reversibly to NS3 with a multistep mechanism. The replicon EC_{50} is 400 nM and a cell-based viral clearance assay showed 3 $\log_{10}$ reductions of viral RNA levels at concentrations above 3.5 μM [18]. With good oral bioavailability and high liver exposure, **14** is slated for clinical studies [18]. The co-crystal structure of **14** shows that it only partially overlaps with the region accessed by BILN-2061, which explains why **14** retains full activity against NS3 mutants (e.g., D168V) that are more than 1000-fold less sensitive to BILN 2061 [19]. Modification of the bicycloproline moiety and the N-terminal capping group as seen in **15**, yields potent derivatives ($IC_{50} < 500$ nM) [20]. Even the replacement of the cyclopentane moiety in **14** with the bulkier bicyclo[2.2.1]hept-2-ene is compatible with good potency [21]. Replacement of norvaline in **14** with difluoro-Abu and methylbenzyl instead of cyclopropyl yields potent anti-viral activity (replicon $IC_{50} = 630$ nM) [22]. Other examples of new α-keto-peptide inhibitors are **16** and **17** [23]. Compounds bearing only an aldehyde group replacing the entire α-keto-amide moiety also show *in vitro* activity in the low micromolar range [24]. Another class of covalent inhibitors is that of the pyrrolidine-*trans*-lactams, exemplified by **18** and **19**. The crystal structure of a smaller example showed that the serine hydroxyl opens the lactam ring, forming a hemiketal [25]. As older compounds in this series exhibited carbamate moieties at the N-terminus, newer designs favor the urea linker. There is crystallographic evidence that both amide hydrogens engage in hydrogen bonding to A157 [26]. **18** and **19** exhibit replicon IC_{50} values of 300 and 100 nM, respectively, although **18** was found to be fivefold more active in the enzyme assay [26]. Due to the chemical instability of the lactam moiety, compounds like **18** and **19** exhibit

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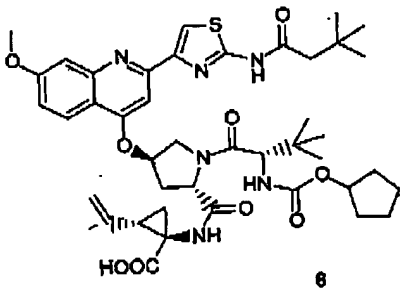
undesirable, fast intravenous (IV) clearance rates. GW0014, **20**, however, although less potent, showed significantly improved *in vivo* pharmacokinetic properties and demonstrated anti-viral activity in a surrogate animal model with GBV-B infected marmosets following subcutaneous administration [27].



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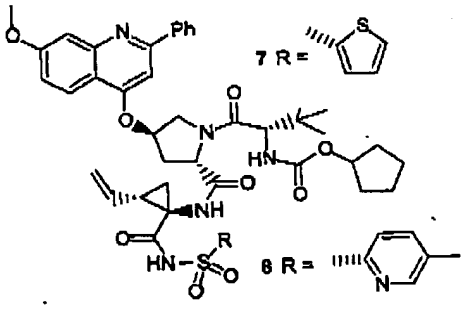

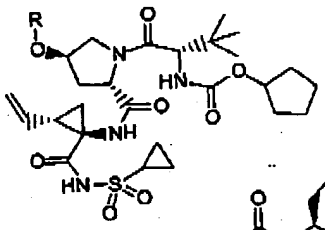

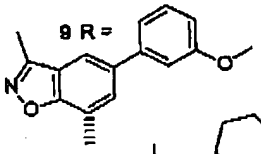

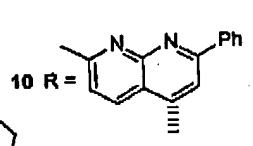

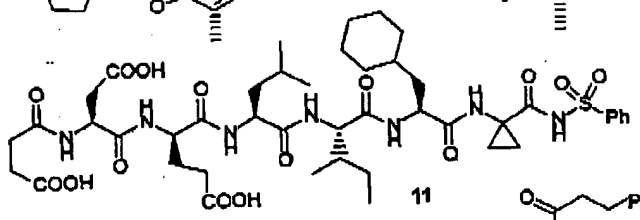

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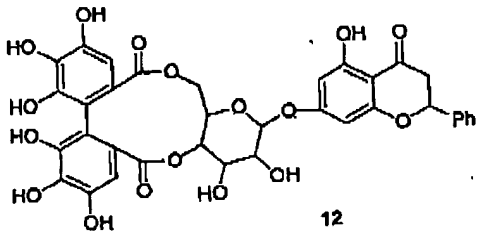

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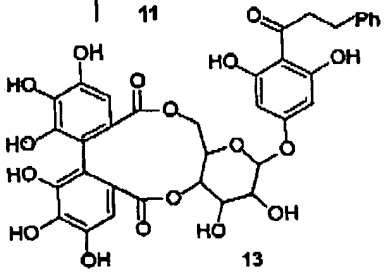

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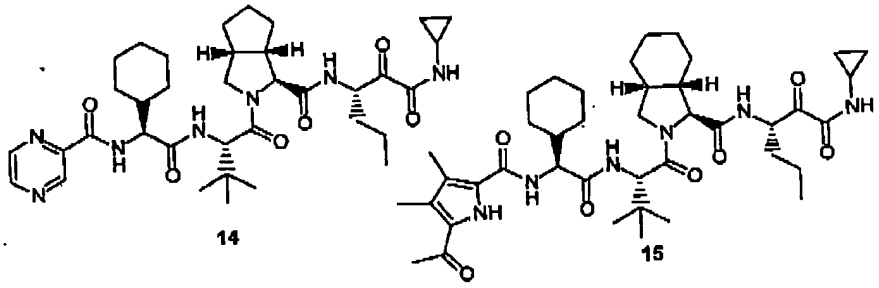

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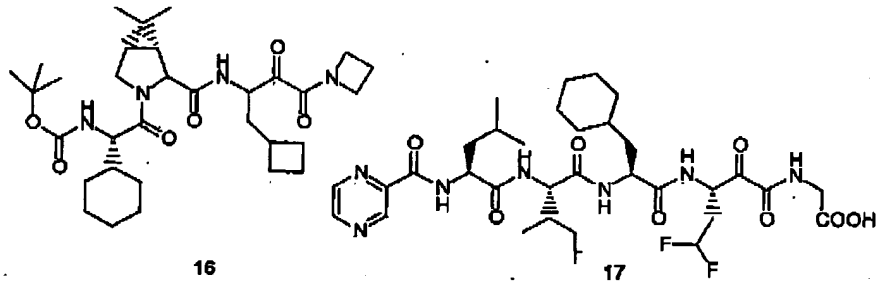

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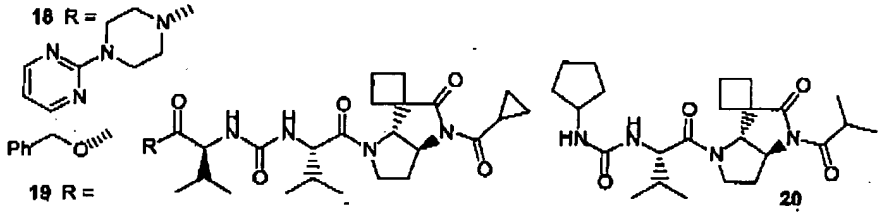

2.2. NS5b RNA dependent RNA polymerase

As an RNA virus, HCV must encode its own RNA dependent RNA polymerase, NS5b [28]. NS5b is essential for viral replication and uses single-stranded HCV RNA as a template to initiate *de novo* synthesis [29]. The enzyme contains a hydrophobic C-terminus which anchors the polymerase to the ER membrane in a replicase complex composed of viral and host proteins [30]. Under enzymatic screening conditions the hydrophobic C-terminus of NS5b causes several important assay complications. The solubility of expressed protein is decreased by the presence of this tail as well as shifts in K_m for both RNA template and nucleotide substrates (Table 1). The usual solution is to truncate this tail as either the Δ21 or Δ57 construct. N- or C-terminal His_6 tags as purification aids can further change the affinities. This has the effect, particularly in the case of some non-nucleoside inhibitors, of causing IC_{50} values to vary dramatically depending on the exact construct used (Table 1) [31].

Furthermore, the choice of homopolymeric vs. heteropolymeric templates with or without primers can further shift the substrate K_ms and consequently the inhibitor's

Table 1. Effect of NS5b enzyme constructs on kinetics and inhibition

	HT[a]-NS5b	HT-NS5bΔ21	NS5bΔ57-HT	NS5bΔ21-HT	NS5b
K_m (P-T)[b] (nM)	210	58	34	25	25
K_m (UTP) (nM)	6200	12,000	1800	5200	3300
IC_{50} (nM)[c]	54	440	2200	3000	5700

[a] His_6-tagged.
[b] Primer-template.
[c] IC_{50} of compound **21**.

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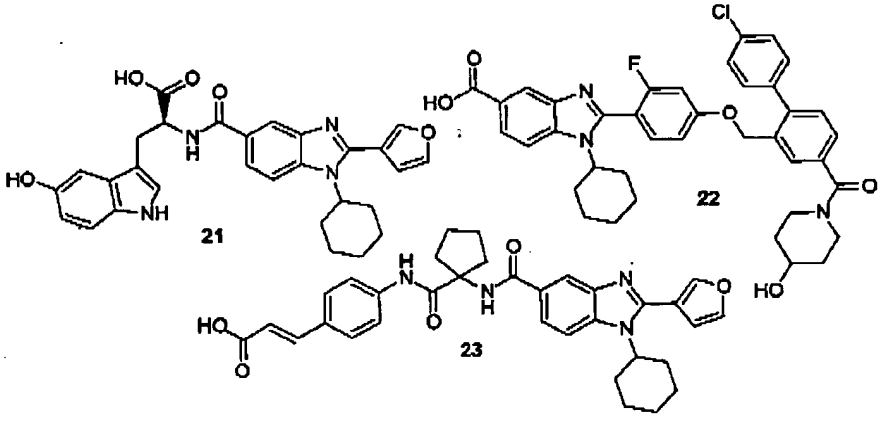
IC_{50}. Therefore one must clearly understand the enzymatic systems of reported results to properly analyze and interpret SAR. Crystal structures of the enzyme reveal similarities to the classic polymerase right-handed model with fingers, thumb and the active site palm subdomains [32,33]. Thus the unique structure, *de novo* mechanism and the absence of a homologous mammalian enzyme should allow potent and selective anti-virals to be discovered. Anti-viral therapy strategies targeting this polymerase have been approached with parallel efforts in both nucleoside and non-nucleoside inhibitor discovery.

2.3. Non-nucleoside NS5b inhibitors

Benzimidazole containing compounds were some of the first non-nucleoside inhibitors discovered to be active against NS5b and to date represent the most potent. **22** was reported to be active at <0.01 μM [34] but under different enzyme assay conditions was reported at 0.28 μM [35] demonstrating the importance of understanding the enzyme and polymer constructs. Similarly, the initially reported IC_{50} of **21** using one enzyme construct was 0.054 μM but using a different construct resulted in a 0.25 μM IC_{50} [31,35]. Kinetic studies show that they are non-competitive with NTP and competitive with the RNA template [31]. Further kinetic analysis demonstrated that **21** and **22** were exclusive inhibitors [36]. Finally, **22** was active in the HCV replicon ($EC_{50} = 0.35$ μM) and multiple resistant replicon mutants generated to **22** displayed a common P495L/A mutation in NS5b [35]. This proline residue is located in a recently reported allosteric GTP binding site [32] and may represent the binding site for this benzimidazole class of compounds. Further optimization of this class of allosteric inhibitors has yielded the optimized analog **23** ($IC_{50} < 0.5$ μM) [37–39] and the tetrazole **24** ($IC_{50} = 0.01$ μM) [40]. Interestingly, replacement of the benzimidazole with a pyrazolo-pyrimidine ring and reversal of its relative orientation (6:5 to 5:6 ring system) resulted in active compounds such as **25** ($IC_{50} < 1$ μM) [41].



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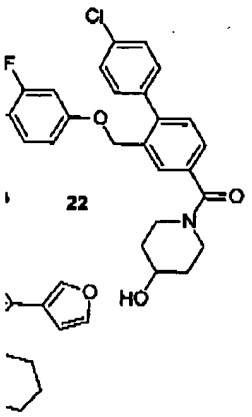

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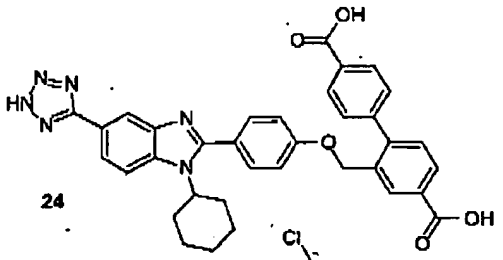

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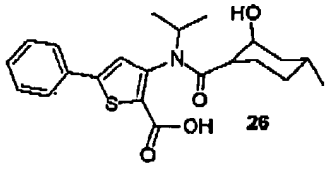

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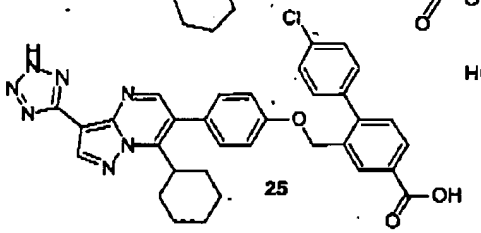

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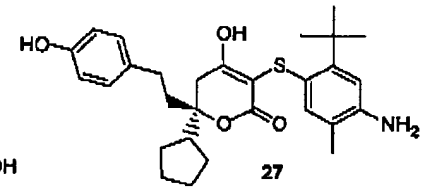
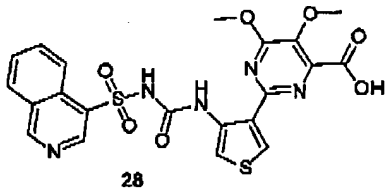


27

A second allosteric binding site has been reported with inhibitors bound to crystalized NS5b [42,43]. Further optimization of one of these two compounds led to the discovery of **26** (NS5b IC_{50} = 0.7 μM, replicon EC_{50} = 0.2 μM). The crystal structure reveals the cyclohexyl ring binding tightly in a deep hydrophobic pocket [44]. Similarly, **27** binds to the same site with the cyclopentyl group binding to the same pocket. Recently, analogs of **27** were reported with activities less than 1 μM [45,46].



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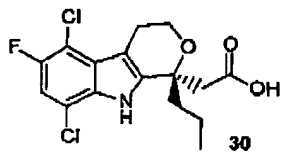

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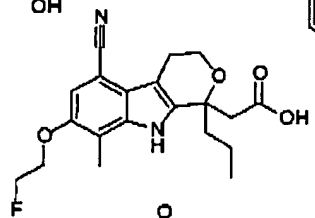

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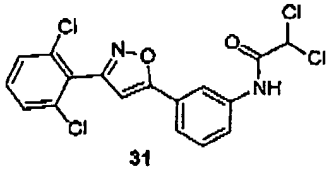

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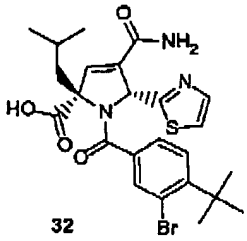

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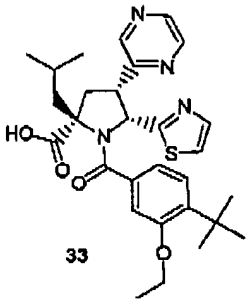

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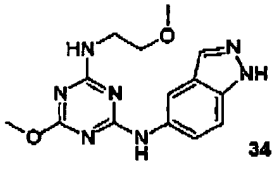

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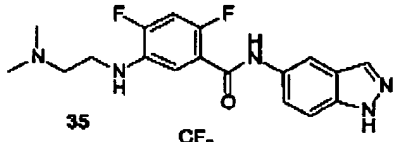

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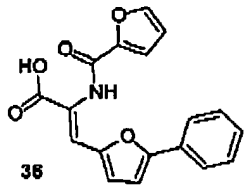

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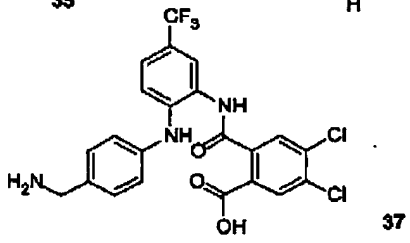

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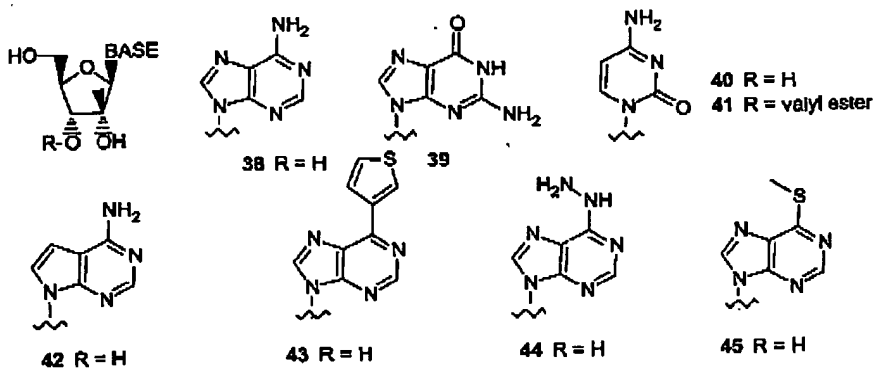
Other non-nucleoside inhibitors have been reported and characterized. A previously described benzothiadiazine (NS5b $IC_{50} = 0.08$ μM, replicon $EC_{50} = 0.5$ μM) was used to generate resistant replicons which mapped the key mutation to M414T, implicating a new inhibitor site on NS5b [47,48]. Similarly, a dimethoxypyrimidine analog **28** previously described [49] was used to generate resistant replicons containing either P156L or G152E mutations [47]. Interestingly, these mutations map the binding site of this compound to the active site, the first reported active-site non-nucleoside inhibitor. A non-nucleoside compound, HCV-371, was reported to have failed a phase I/II clinical trial [28,50]. While the compound was safe, it failed to reduce HCV RNA levels. However, follow-up compounds such as racemic **29** and (*R*)-pyranoindole **30** (NS5b $IC_{50} = 0.004$ and 0.06 μM, respectively) have recently been reported [51,52]. An analog of dichloroacetamide **31**, R803, is active in the replicon ($EC_{50} < 10$ μM) and is claimed to be an NS5b inhibitor [53]. Phase I results for this compound were reported and a phase I/II study scheduled to assess anti-viral efficacy [54]. Dihydropyrroles such as **32** (NS5b $IC_{50} < 5$ μM for best compounds) and related pyrrolidine analogs such as **33** (NS5b $IC_{50} < 0.3$ μM for best compounds) have been reported [55–57]. Triazine **34** (%inhibition at 0.1 μg/mL: HCV NS5b = 46% and HBV RT = 52%) and difluorobenzamide **35** (%inhibition at 0.1 μg/mL: HCV NS5b = 46% and HBV RT = 48%) are two reported promiscuous inhibitors with activity against both HCV NS5b and HBV RT [58,59]. Finally, compounds such as **36** (NS5b $IC_{50} < 10$ μM for best compounds) [60] and 1,2-diaminophenyl compound **37** (NS5b $IC_{50} = 1.42$ μM) have recently been disclosed [61].

2.4. Nucleoside NS5b inhibitors

Nucleoside anti-virals are pro-drugs in that they are actively transported into cells and then activated by cellular kinases to the nucleotide triphosphate. This NTP is now able to competitively inhibit the enzyme or, more commonly, act as a substrate and be incorporated into the nascent RNA chain. Chemical or structural features of

the incorporated nucleoside subsequently prevents (chain-terminates) the further replication of the viral genome. While nucleoside inhibitors can vary in either (or both) the ribose or base portion of the molecule, the initially reported anti-HCV inhibitors were modified ribose analogs such as 2′-fluoro [62], 4′-azido [63] and dioxolane cytidine analogs [64].

To date, the most significant amount of work has been reported on 2′-methylribose nucleosides. Adenosine (**38**, $IC_{50} = 1.9\ \mu M$, $EC_{50} = 0.17\ \mu M$) and guanosine (**39**, $IC_{50} = 0.13\ \mu M$, $EC_{50} = 1.4\ \mu M$) analogs inhibit both NS5b (as the NTP) and the HCV replicon [65]. Mechanism of action work clearly demonstrates that these nucleosides act as chain-terminators. Modeling of **38** into the RNA primer portion of the NS5b crystal structure suggests how these 3′-hydroxyl containing nucleosides are able to act as chain-terminators. The 2′-methylribose nucleoside is incorporated as a substrate but the 2′-methyl group prevents subsequent incorporation *via* steric clashes with either the O4′ or H8 of purines of the incoming nucleotide. Resistant replicons were generated against **38** and showed a S282T mutation in the NS5b sequence. When this mutation is modeled with **38** into the crystal structure, the addition of a methyl group to the wild-type serine (i.e., threonine) clearly prevents the incorporation of this nucleotide into the resistant mutant [65]. The cytidine analog (**40**) is claimed to be active *in vitro* as the active metabolite of its 3′-valyl ester NM-283 (**41**) [66,67] which is currently undergoing a phase Ib/phase IIa clinical trial. Initial data from a 50 patient study (doses from 25 to 800 mg) demonstrated an approximately 0.5 $\log_{10}$ reduction in HCV RNA levels after 100 mg once-daily dosing for 15 days. Clinical pharmacokinetics at both day 1 and 15 showed a half-life slightly longer than 4 h with no apparent accumulation [66,68].



Recently, base modified analogs containing 2′-methylribose have been reported, including the tubercidin (**42**) and 6-thiophene-purine (**43**) [69,70]. Multiple modified-base nucleosides including a hydrazine analog series of **44** and thiomethylpurine analog **45** were reported to have HCV replicon EC_{50}s less than 10 μM [71–74]. Mouse PK data for **45** demonstrated half-lives of 1.2 h and 0.43 h for oral and IV dosing, respectively, with no toxicity observed up to 160 mg/kg.

2.5. Other viral targets

HCV IRES inhibitors are mostly nucleic acid based molecules and no small molecule with promising activity has been reported. The only inhibitor that has demonstrated clinical effectiveness is ISIS 14803 (anti-sense oligonucleotide). In a phase II trial involving 43 patients with chronic hepatitis C, ISIS 14803 reduced viral loads in 7 patients from ≥ 1 to 3.8 $\log_{10}$ copies/ml during a 12-week treatment period [75]. Gene silencing by RNA interference is being explored as a new approach to inhibit HCV replication. Duplex small interfering RNAs directed at the HCV genome has been shown to be effective in dramatically inhibiting HCV replication and protein expression in human hepatoma cells [76]. *In vivo* application is likely to require gene delivery.

Despite certain efforts in targeting the HCV NS3 helicase, no compound that selectively and directly inhibits the NS3 ATP-hydrolyzing or nucleic acid-unwinding activities has been reported. Several nucleoside compounds including ring-expanded nucleosides **46–48** were synthesized and evaluated for their abilities to affect helicases of *Flaviviridae* viruses. Mixed results were obtained. The compounds can cause either enzyme inhibition or activation depending on the assay condition, source of the enzyme and nucleic acid template [77]. While these compounds may be interesting tools to elucidate putative allosteric sites on the helicase, their ability to inhibit HCV replication remains to be shown.

The HCV P7 protein forms an ion channel in lipid bilayers. It is not essential for viral replication, but it has been speculated that cation permeation across membranes may be important for the maturation and release of infectious virions. There is interest in evaluating P7 as an anti-viral target. Amantidine, **49**, an anti-influenza agent that inhibits the ion channel of influenza virus, inhibits the HCV P7 ion channel [78]. Amantidine has been tested clinically against HCV and as a single agent has not shown anti-viral activity; in combination with interferon or interferon and ribavirin has yielded mixed results [79,80]. Long-alkyl-chain iminosugar derivatives inhibit bovine viral diarrhea virus (BVDV). **50–52** were recently shown to inhibit the HCV P7 ion channel in black lipid membrane [81].

3. INHIBITORS FOR NON-VIRAL TARGETS

3.1. Caspase

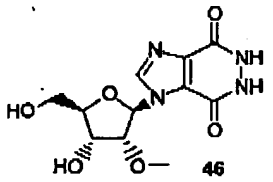
Liver disease caused by conditions such as HCV infection is characterized by excessive apoptosis. Oxamyl dipeptide IDN-6556 is an anti-apoptotic irreversible caspase inhibitor with potencies against several caspases in the low to subnanomolar range [82]. In a phase IIa trial with chronic hepatits C patients, oral dosing of IDN-6556 for 14 days significantly lowered liver enzyme levels in plasma at all doses [83]. While IDN-6556 is not an anti-viral agent, it may help infected patients to preserve the function and health of their livers.

3.2. Toll-like receptor 7

Certain C8-substituted and N7, C8-substituted guanosine analogs stimulate immune responses. Some of these compounds activate toll-like receptor 7 (TLR7), a member

PAGE 48/53 * RCVD AT 5/1/2006 9:12:47 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/19 * DNIS:2738300 * CSID:6174394170 * DURATION (mm-ss):15-02

of a group of receptors that take part in the host defense against viruses. Isotoribine (53, ANA245) is a TLR7 agonist that is currently under evaluation in the clinic and so is its oral pro-drug ANA971 [84]. While it has no direct anti-viral activity, it induces hepatic 2′,5′-oligoadenylate synthetase (OAS) leading to activation of the innate immune response. In a phase Ib trial with a 7-day treatment by IV administration, the compound reduced viral load in patients with chronic HCV infection. Viral load reduction was maximal in the 800 mg arm at approximately 1–3 $\log_{10}$ copies/ml and was associated with induction of the OAS system [85].



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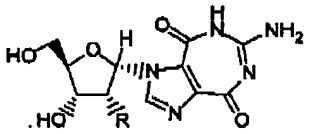
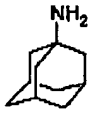


47 R = OH
48 R = H



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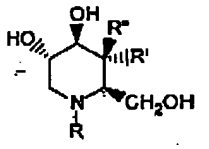
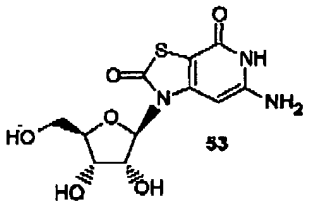


50 R = C_9H_{19}, R′ = OH, R″ = H
51 R = C_9H_{19}, R′ = H, R″ = OH
52 R = $C_6H_{12}OC_2H_5$, R′ = H, R″ = OH



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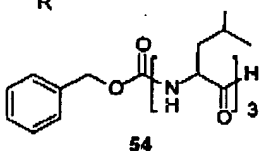

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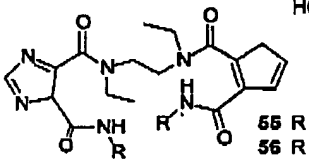

55 R = L-Leu-O-benzyl ester
56 R = L-Val-O-benzyl ester

3.3. Proteasome inhibitors

A fortuitous discovery recently implicated the human 20S proteasome subunit α-PSMA7 in HCV IRES mediated translation. In fact, a proteasome inhibitor MG132 54 showed dose-dependent inhibition of HCV IRES activity in human hepatoma cells [86].

3.4. CD81

CD81 is a member of the tetraspanin family of integral membrane protein and is thought to be a binding partner for the HCV envelope E2 protein. Although binding alone is not enough for infection, prevention of binding does coincide with lack of infection in human hepatocytes. An extracellular region (D helix) on CD81 is important for binding to E2. Small molecule mimics 55, 56 of the D helix inhibit binding of E2 to CD81 on Molt-4 cells [87]. Cellular activities of these compounds are unknown and may be difficult to determine since they require 6% DMSO for solubilization.

4. CONCLUSION

There has been a dramatic increase in patents and publications describing new HCV inhibitors last year as many research organizations have turned their attention to this important viral disease. Compounds which directly target viral specific proteins are beginning to enter clinical trials and the recent encouraging proof-of-principle results with BILN 2061 will hopefully mark the beginning of an era of new high efficacy treatments for HCV.

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